

GLP-1 Receptor Agonists and Female Reproductive Health: Mechanisms Underlying Endocrine, Ovarian, and Oocyte-Related Modifications

Panayiotis Michael Zavos, Ed.S., Ph.D., MBA, HCLD^{1*}, Carmen Teresa Navarro, MD, Ph.D², Pedro Torrecillas Cabrera, MD, Ph.D³, Cesare Aragona, MD, Ph.D⁴, Maria Salomé Bezerra-Espínola, Ph.D⁵, Ritu Santwani, MD⁶, Shady Abdelsattar Saleem, MD⁷ and Denisa Protopopescu, MD, Ph.D⁸

¹Professor, University of Kentucky & Director of Andrology, Andrology Institute of America, Lexington, Kentucky, USA.

²Women Care Center, Centro Comercial Terras Plaza, Caracas, Venezuela.

³Chief of Urology & Andrology, Urology Clinic, Malaga, Spain.

⁴Former Chief Gynecology, Sapienza University of Rome, Italy.

⁵Guglielmo Marconi University (Unimarconi), Rome, Italy.

⁶Founder and Medical Director of 360° Healthcare Studio, Pune, India.

⁷Chief of Gynecology and In Vitro Fertilization, Cairo, Egypt.

⁸Central Medical International Bucuresti, Fertility Clinic, Bucurest, Romania.

ABSTRACT

Background and Objectives: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly used by women of reproductive age, given the close relationship between energy balance, insulin sensitivity, ovarian steroidogenesis, and fertility. This narrative review synthesizes human, mechanistic, and regulatory evidence on how GLP-1 signaling and GLP-1RA treatment may influence the female reproductive axis, focusing on obesity, polycystic ovary syndrome (PCOS), menstrual function, follicular biology, assisted reproduction, and reproductive safety, and clarifies which claims are supported by direct human endpoints versus mechanistic plausibility alone.

Materials and Methods: A structured, non-systematic search of PubMed/MEDLINE, Embase, and the Cochrane Library was conducted for records published between January 2014 and September 2026, supplemented by reference-list screening and current prescribing information. Studies were stratified by evidence level using GRADE certainty principles for pooled endpoints and Oxford Centre for Evidence-Based Medicine (OCEBM) levels for individual study designs.

Results: The strongest human evidence concerns women with PCOS and/or obesity, in whom liraglutide and exenatide have been associated with weight reduction and improvements in menstrual frequency and short-term spontaneous pregnancy rates. However, later follow-up and a 2026 meta-analysis rated as low-certainty evidence show heterogeneous reproductive effects, and evidence for live birth, ovarian reserve, and direct oocyte benefit remains inadequate. Experimental studies suggest GLP-1 signaling may modify granulosa-cell inflammation and follicular development, but this does not prove that GLP-1RAs improve human oocyte competence. Current labeling recommends discontinuing semaglutide before planned pregnancy and tirzepatide once pregnancy is recognized; emerging pregnancy safety data are reassuring but still insufficient to establish routine safety.

Conclusions: GLP-1RAs should presently be viewed as metabolic and preconception tools for selected women with obesity-related reproductive dysfunction, especially PCOS, rather than as established fertility or oocyte-quality therapies, and metabolic optimization before conception must be clearly distinguished from pharmacological treatment during pregnancy.

KEYWORDS

GLP-1 receptor agonists, Female reproductive health, Fertility, Polycystic ovary syndrome, Obesity, Insulin resistance, ovulation; oocyte, IVF, Pregnancy safety.

Panayiotis Michael Zavos

Professor, University of Kentucky, Director of Andrology, Andrology Institute of America, Lexington, Kentucky, USA.

Received: August 15, 2026; **Accepted:** September 17, 2026; **Published:** September 27, 2026

Copyright: © 2026 ASRJS. This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International license.

Citation: Panayiotis Michael Zavos, Carmen Teresa Navarro, Pedro Torrecillas Cabrera, Cesare Aragona, Maria Salomé Bezerra-Espínola. GLP-1 Receptor Agonists and Female Reproductive Health: Mechanisms Underlying Endocrine, Ovarian, and Oocyte-Related Modifications. *Int J Nurs Health Care*. 2026; 2(5):1-16.

Review Approach and Scope

Search Strategy and Selection Criteria

This manuscript was designed as a structured narrative review rather than a systematic review or meta-analysis. The original paper was retained as the conceptual foundation and expanded with recent peer-reviewed literature and authoritative prescribing information.

PubMed/MEDLINE, Embase, and the Cochrane Library were searched for records published between January 1, 2014, and September 5, 2026, the latter date corresponding to the search closure prior to manuscript finalization. The following representative Boolean strings were used, combined with database-specific filters for humans and English language where applicable, and adapted with MeSH terms and truncation as appropriate to each database:

(1) ("glucagon-like peptide-1 receptor agonist*[tiab] OR "GLP-1 RA"*[tiab] OR liraglutide[tiab] OR semaglutide[tiab] OR exenatide[tiab] OR dulaglutide[tiab] OR tirzepatide[tiab] OR "dual GIP/GLP-1 receptor agonist"*[tiab]) AND ("polycystic ovary syndrome"[tiab] OR PCOS[tiab] OR "female reproduct*" [tiab] OR fertility[tiab] OR infertility[tiab] OR ovulation[tiab] OR "ovarian function"[tiab] OR "granulosa cell*" [tiab] OR oocyte[tiab] OR IVF[tiab] OR "assisted reproduct*" [tiab]).

(2) ("GLP-1 receptor agonist*" [tiab] OR liraglutide[tiab] OR semaglutide[tiab] OR tirzepatide[tiab]) AND (pregnancy[tiab] OR "pregnancy outcome*" [tiab] OR lactation[tiab] OR "congenital malformation*" [tiab] OR teratogenic* [tiab] OR "adverse event*" [tiab] OR pharmacovigilance[tiab] OR "FDA Adverse Event Reporting System" [tiab] OR FAERS[tiab]).

(3) ("GLP-1 receptor" [tiab] AND (ovary[tiab] OR ovarian[tiab] OR follicle[tiab] OR "granulosa cell*" [tiab] OR steroidogenesis[tiab] OR CXCL10[tiab] OR connexin* [tiab])) for cellular and animal mechanistic studies.

Reference lists of eligible systematic reviews and included primary studies were manually screened for additional relevant records,

and current U.S. Food and Drug Administration prescribing information was consulted directly for regulatory and labeling positions.

Inclusion and Exclusion Criteria

Eligible records included: (a) randomized controlled trials, observational cohort studies, and systematic reviews or meta-analyses reporting reproductive, endocrine, or pregnancy-related outcomes in women exposed to GLP-1RAs or dual GIP/GLP-1 receptor agonists; (b) cellular, follicular, or animal mechanistic studies directly addressing GLP-1 signaling in ovarian or reproductive tissue; and (c) regulatory prescribing information and pharmacovigilance analyses addressing reproductive safety. Records were required to be published in English, available as full text, and to report a reproductive, endocrine, obstetric, or safety endpoint relevant to the four review questions outlined below.

Records were excluded if they: (a) addressed GLP-1RA use exclusively in men or in non-reproductive-age populations without extractable female reproductive data; (b) were conference abstracts, editorials, or commentaries without original data; (c) were case reports describing fewer than five patients, given their limited generalizability for the clinical claims addressed in this review; (d) duplicated data already reported in a more complete or updated publication by the same research group; or (e) could not be retrieved in full text through institutional or open-access channels.

Primary human studies were prioritized for clinical conclusions, while mechanistic and animal studies were used to contextualize biological plausibility; regulatory prescribing information was used specifically to establish current safety and labeling positions. The evidence base was intentionally stratified into human randomized trials and observational studies, systematic reviews and meta-analyses, cellular and follicular experiments, animal studies, and regulatory documents. This distinction is important because the same biological question can produce very different levels of evidentiary certainty depending on whether the endpoint is measured in a cultured granulosa cell, a mouse follicle, a clinical pregnancy, or a live birth.

Evidence Grading Framework

To anchor the qualitative evidence-strength judgments used throughout this review, individual study designs were classified using the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (e.g., Level 1b for individual randomized trials, Level 2b for individual cohort studies, Level 3b for case-control or pharmacovigilance disproportionality analyses, Level 5 for mechanistic and animal studies); these levels are reported explicitly for each study in Table 1. Where a source meta-analysis itself reported a formal GRADE (Grading of Recommendations Assessment, Development and Evaluation) certainty rating for a pooled estimate, that rating is cited directly in the text (e.g., the 2026 PCOS meta-analysis, which rated its principal findings as low-certainty evidence). The qualitative evidence-strength summary in Table 3 reflects the authors' synthesis of these study-level and pooled-evidence considerations rather than a formal, independently conducted GRADE Summary-of-Findings assessment.

Particular emphasis was placed on evidence published through 2026 because the clinical literature is evolving rapidly. Recent systematic reviews have expanded the field beyond early liraglutide and exenatide studies, while newer reviews have highlighted the unresolved questions surrounding fertility treatment timing and pregnancy exposure [1-5]. The purpose is not to imply that recent reviews supersede primary studies, but to use them to contextualize the direction, consistency, and limitations of the underlying evidence.

How this review differs from recent syntheses. The field now includes several substantive 2025–2026 contributions, including a mechanistic systematic review integrating IVF data and ovarian physiology [1], a systematic review and meta-analysis in PCOS [2], a narrative review of fertility restoration and reproductive safety [3], a review addressing what is currently known about GLP-1RAs and fertility [4] and a narrative review with an investigational pilot survey of patient perspectives in academic reproductive endocrinology [5]. Earlier reviews emphasized metabolic and PCOS-related outcomes, whereas these more recent syntheses have incorporated molecular ovarian mechanisms, pregnancy-exposure data, and clinician or patient perspectives. The present review focuses specifically on the translational boundary between systemic metabolic benefit, ovarian signaling, and clinically meaningful oocyte and embryo outcomes, while emphasizing treatment timing as a determinant of interpretation and distinguishing preconception metabolic benefit from direct ovarian or oocyte claims and from pregnancy safety.

The review therefore asks four linked questions: (1) how does metabolic dysfunction impair female reproductive function; (2) through which pathways could GLP-1 signaling modify that dysfunction; (3) what reproductive outcomes have actually been demonstrated in humans; and (4) how should potential preconception benefits be reconciled with the current uncertainty surrounding pregnancy exposure? This framework prevents a

common interpretive error—treating a reduction in body weight, a more regular menstrual cycle, an increase in pregnancy rate, and an improvement in oocyte competence as though they were equivalent endpoints.

Introduction

Female reproductive capacity is not independent of systemic metabolic health. The hypothalamic-pituitary-ovarian (HPO) axis continuously integrates nutritional state, energy availability, endocrine feedback, and gonadal function. Obesity and insulin resistance can disturb this coordination through altered gonadotropin signaling, hyperinsulinemia, androgen excess, adipokine and inflammatory changes, altered steroid metabolism, and impaired follicular function [6-8]. The resulting phenotype may range from subtle changes in cycle characteristics to oligo-ovulation, anovulation, subfertility, and poorer outcomes during assisted reproduction.

PCOS is an especially informative clinical model because reproductive and metabolic abnormalities coexist. Insulin resistance can amplify ovarian androgen production and reduce hepatic sex hormone-binding globulin (SHBG), increasing the free androgen fraction. Adipose tissue contributes additional endocrine and inflammatory signals, while altered follicular sensitivity to gonadotropins may contribute to follicular arrest [6-9]. These processes are not necessarily independent: hyperandrogenism, insulin resistance, obesity, and chronic low-grade inflammation can reinforce one another, producing a reproductive phenotype that is difficult to reverse by targeting a single pathway.

GLP-1 is biologically relevant at this intersection. Endogenous GLP-1 is a nutrient-responsive hormone with established actions on insulin secretion, glucagon suppression, gastric emptying, appetite, and energy balance. GLP-1RAs reproduce or prolong these effects and can produce substantial metabolic changes [10]. The reproductive question is whether their observed effects are simply downstream consequences of improved metabolic health or whether GLP-1 signaling also acts directly within central reproductive circuits, ovarian cells, follicles, endometrium, or other reproductive tissues.

A terminological clarification is warranted before proceeding. Liraglutide, semaglutide, and exenatide are true GLP-1 receptor agonists (GLP-1RAs), whereas tirzepatide is pharmacologically distinct: a dual GIP/GLP-1 receptor agonist that also engages the glucose-dependent insulinotropic polypeptide receptor. Because the reproductive literature increasingly includes tirzepatide, this review uses "GLP-1-based therapies" as the broad umbrella term when referring to the class collectively, and reserves "GLP-1RA" specifically for single-receptor GLP-1 agonists, introducing "dual GIP/GLP-1 receptor agonist" where the distinction is clinically relevant. Network meta-analyses comparing multiple agents within this drug class confirm that weight-loss efficacy differs meaningfully across individual GLP-1RAs and polyagonists, reinforcing the need for agent-specific rather than class-level

interpretation of reproductive findings [11].

The distinction matters clinically. If reproductive improvement is primarily secondary to weight loss and improved insulin sensitivity, GLP-1RAs may be useful as a bridge to a healthier preconception state but should not be described as direct fertility drugs. If direct ovarian actions exist, they could theoretically influence follicular development even when weight change is similar between treatment groups. Current evidence supports both possibilities but does not establish their relative contribution [1].

The reproductive implications of GLP-1 signaling can be conceptualized as a network rather than a single pathway, spanning central metabolic effects, endocrine effects on androgen availability and gonadotropin-dependent ovarian function, and local ovarian signaling affecting granulosa-cell behavior and the follicular microenvironment; this network is summarized in Figure 1 at the end of the following section. The strength of evidence differs substantially across these levels.

GLP-1 Biology and the Female Reproductive Axis

Canonical GLP-1 physiology

GLP-1 is produced predominantly by intestinal L cells and participates in postprandial glucose regulation. Its short endogenous half-life has limited direct therapeutic utility, whereas long-acting receptor agonists such as liraglutide and semaglutide maintain receptor stimulation for clinically useful periods. The principal metabolic effects—glucose-dependent insulin secretion, suppression of glucagon, delayed gastric emptying, and reduced energy intake—create a physiological context in which chronic hyperglycemia and excessive energy storage can be reduced.¹² These canonical effects describe single-receptor GLP-1RAs; tirzepatide, as a dual GIP/GLP-1 receptor agonist, engages an additional incretin pathway, and its metabolic and reproductive effects should not be assumed to be quantitatively or qualitatively identical to those of single-receptor agents unless specifically demonstrated.

These effects are particularly relevant to reproductive physiology because ovarian function is sensitive to metabolic signals. The follicle requires coordinated substrate availability, insulin signaling, gonadotropin responsiveness, and steroidogenesis. Excessive metabolic stress can therefore alter reproductive function without requiring structural ovarian disease. This provides a plausible explanation for why reproductive outcomes may improve after metabolic therapy even when no direct ovarian drug action is demonstrated.

Receptor distribution and interpretation of localization studies

GLP-1 receptor localization studies have identified expression in multiple tissues, and reproductive relevance has been proposed from experimental observations in central and peripheral systems [6,10]. However, receptor detection must be interpreted cautiously. Immunohistochemical localization does not establish receptor abundance under physiological conditions, does not prove that a

receptor is functionally coupled to a clinically relevant pathway, and does not establish that therapeutic concentrations of an agonist produce a meaningful tissue-level effect. Most receptor-localization data underlying this literature were generated using single-receptor GLP-1 ligands or antibodies; comparatively little tissue-level localization data specifically address the dual GIP/GLP-1 receptor engaged by tirzepatide, so conclusions about receptor distribution in reproductive tissue should be read as pertaining primarily to the GLP-1 receptor itself rather than to dual agonism generally.

This distinction is especially important in the ovary. A direct action would require more than receptor presence: there should be evidence of pharmacologically relevant signaling, a reproducible cellular response, a coherent downstream mechanism, and ideally a clinical phenotype that persists after accounting for weight loss and metabolic improvement. Current ovarian evidence is strongest at the mechanistic and translational levels rather than at the level of definitive human fertility outcomes [1].

The ovary as a metabolic and endocrine organ

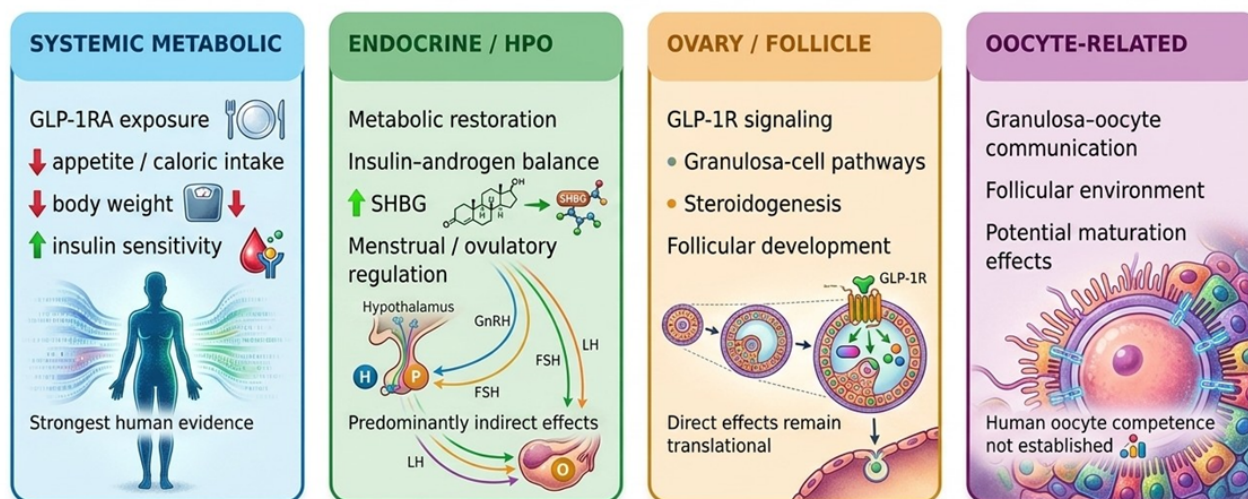
The ovarian follicle is a dynamic functional unit composed of the oocyte, cumulus and mural granulosa cells, theca cells, stromal elements, follicular fluid, vasculature, and extracellular matrix. Granulosa cells respond to FSH and, during the periovulatory period, to LH-related signaling. They convert theca-derived androgens into estrogens through aromatase activity and maintain bidirectional communication with the oocyte through gap junctions and paracrine factors. Disruption at any point in this network can impair follicular selection, steroidogenesis, meiotic maturation, or ovulation.

GLP-1RA treatment could influence this system indirectly by changing the metabolic environment surrounding the follicle. A reduction in insulin resistance may decrease the insulin-mediated amplification of ovarian androgen production, while weight loss may alter adipose-derived inflammatory and endocrine signals. Direct cellular effects are also biologically plausible, but they remain more difficult to establish because ovarian cells are simultaneously exposed to systemic metabolic changes.

Figure 1 summarizes the reproductive implications of GLP-1 signaling discussed in this section, conceptualized as a network rather than a single pathway. Central metabolic effects can alter energy balance and insulin sensitivity; endocrine effects can modify androgen availability and gonadotropin-dependent ovarian function; and local ovarian signaling may influence granulosa-cell behavior and follicular microenvironment. The strength of evidence differs substantially across these levels.

Obesity, Insulin Resistance, and Reproductive Dysfunction

The association between obesity and female reproductive dysfunction is multifactorial. Clinical and experimental literature implicates altered HPO-axis signaling, insulin resistance, androgen excess, adipose-tissue inflammation, altered leptin and adipokine signaling, and changes in ovarian and endometrial physiology



Conceptual model: metabolic effects are clinically established; direct ovarian and oocyte effects remain less certain.

Figure 1: GLP-1 signaling across the female reproductive axis.

[Source: Conceptual synthesis based on refs. [1,6,10,12,13]; arrows indicate proposed pathways rather than established causal relationships.]

[7,8]. Obesity does not necessarily produce complete anovulation; rather, reproductive effects may occur along a spectrum, with altered gonadotropin dynamics and cycle characteristics occurring even in some women who continue to ovulate.

Insulin resistance is particularly important because hyperinsulinemia can act directly on ovarian steroidogenic pathways while simultaneously reducing hepatic SHBG synthesis. The resulting increase in free androgen exposure may interfere with normal follicular development. In PCOS, this interaction can reinforce theca-cell androgen production and follicular arrest. The reproductive consequence is not simply “excess weight,” but a network of metabolic and endocrine disturbances that influence the follicle and HPO axis.

Independent of pharmacological therapy, lifestyle-based weight-loss interventions—including structured exercise and dietary modification—have themselves been associated with improved fertility outcomes and fewer pregnancy complications in women with overweight or obesity, providing a non-pharmacological benchmark against which GLP-1RA-specific effects should be compared [14,15]. A network meta-analysis directly comparing exercise, diet, and pharmacological interventions similarly found that combined approaches produced the most consistent improvements in BMI, ovulatory function, and hormonal profile among reproductive-aged women with overweight or obesity [16].

Weight reduction can therefore have reproductive consequences independent of any specific anti-obesity drug. Improvements in insulin sensitivity, glycemic regulation, inflammatory tone, androgen exposure, and physical activity may all contribute. Contemporary reproductive reviews emphasize that obesity treatment should be integrated with fertility planning rather than

considered separately from it [17,18].

GLP-1RA Effects on Endocrine Function Insulin sensitivity and androgen physiology

The most defensible mechanism linking GLP-1RA treatment to reproductive improvement is metabolic. By reducing energy intake and improving glycemic physiology, GLP-1RAs can reduce the metabolic burden associated with obesity and insulin resistance. In women with PCOS, this may lessen hyperinsulinemic stimulation of ovarian androgen production and may increase SHBG, thereby reducing free androgen exposure. The magnitude of each endocrine change varies across studies and should not be assumed to occur uniformly in all women.

Importantly, the endocrine response is phenotype dependent. A woman with obesity, insulin resistance, and hyperandrogenic PCOS has a greater mechanistic opportunity for improvement than a lean, metabolically healthy woman with an unrelated infertility diagnosis. This distinction is central to interpreting the clinical literature: most reproductive trials have focused on women with PCOS and/or overweight or obesity, so their findings should not automatically be generalized to the broader infertility population [1-4].

Menstrual cyclicity

Menstrual regularity is a clinically useful intermediate outcome because persistent oligo-ovulation is a major pathway to infertility in PCOS. In a double-blind randomized trial, Nylander and colleagues assigned 72 women with PCOS in a 2:1 ratio to liraglutide 1.8 mg/day or placebo. The trial reported improvement in menstrual frequency with liraglutide, providing evidence that GLP-1RA treatment can modify ovarian dysfunction in this population [19]. The study was not designed to establish live birth

benefit, and the menstrual endpoint should therefore be interpreted as evidence of improved reproductive physiology rather than proof of increased cumulative fertility.

A broader synthesis is more cautious. A 2023 systematic review and meta-analysis of 11 randomized trials involving 840 women with PCOS (469 receiving a GLP-1RA, 371 controls) reported an improved natural pregnancy rate (RR 1.72, 95% CI 1.22–2.43; $I^2=0\%$, indicating consistent effects across trials) and improved menstrual regularity (SMD 1.72, 95% CI 0.60–2.85; $I^2=95.6\%$, indicating substantial heterogeneity that should temper confidence in the pooled menstrual estimate), but evidence for several reproductive outcomes was otherwise limited [20]. A 2026 systematic review and meta-analysis, prospectively registered (PROSPERO CRD42024535096) and screening 9,654 records to identify 11 eligible RCTs, found a modest short-term BMI reduction with GLP-1RAs used as add-on therapy (mean difference -1.38 kg/m^2 , 95% CI -2.39 to -0.38), explicitly rated as low-certainty evidence under GRADE, while evidence for glucose, insulin, hirsutism, and menstrual regularity was graded as insufficient to support conclusions; no eligible data were identified for quality of life or cost-effectiveness [2]. These differences illustrate how conclusions can change when the question shifts from individual positive trials to pooled evidence.

Ovulation and the distinction between cycle regularity and fertility

A more regular menstrual cycle does not necessarily prove normal ovulation in every cycle. Menstrual bleeding can occur without robust ovulatory function, and cycle regularity is therefore an imperfect surrogate. Recent systematic work has emphasized that direct ovulation assessment has not been consistently performed across the GLP-1RA literature [1,2]. This is a critical methodological issue because the causal chain from therapy to fertility is more convincing when studies measure follicular development, ovulation, conception, and live birth as separate endpoints.

The practical implication is that GLP-1RAs should not be described as ovulation-induction drugs. The 2023 international PCOS guideline recommends letrozole as first-line pharmacological ovulation induction for infertile anovulatory women with PCOS when no other infertility factor is present [9]. GLP-1RA therapy occupies a different conceptual position: it may improve the metabolic and endocrine conditions that make ovulation more likely, but it does not replace evidence-based ovulation induction when treatment is indicated.

Ovarian and Follicular Mechanisms

Granulosa-cell biology

Granulosa cells are a plausible site at which systemic metabolic changes and local GLP-1-related signaling could converge. These cells regulate follicular growth, estrogen synthesis, apoptosis and survival, extracellular matrix remodeling, and communication with the oocyte. In PCOS, inflammatory signaling and abnormal follicular microenvironments may contribute to impaired follicular

development.

A 2024 translational study investigated granulosa cells from women with PCOS and used RNA sequencing, follicular-fluid analysis, molecular assays, and a mouse ovarian follicle culture system. Liraglutide reduced inflammatory signaling, with CXCL10 emerging as a prominent target. The investigators linked CXCL10-related signaling to changes in connexin-43/GJA1 and JAK2-associated pathways and reported improved follicular development in experimental systems [13].

This study is important because it provides a mechanistic bridge between clinical observations and ovarian biology. It also illustrates the limits of mechanistic inference. Human granulosa-cell findings, cultured mouse follicles, and clinical reproductive outcomes are not interchangeable forms of evidence. The study does not demonstrate that liraglutide improves human oocyte euploidy, embryo development, implantation, or live birth. Instead, it supports a testable hypothesis that inflammatory signaling within the follicular microenvironment may be modifiable by GLP-1RA exposure. Notably, this translational study used liraglutide, a single-receptor GLP-1RA; whether dual GIP/GLP-1 receptor agonism produces comparable granulosa-cell effects has not been directly tested and should not be assumed.

Steroidogenesis

Ovarian steroidogenesis depends on coordinated theca-cell androgen production and granulosa-cell aromatization. Insulin can potentiate ovarian steroidogenic activity, while hyperandrogenism can disturb follicular selection and maturation. GLP-1RA treatment may therefore influence steroidogenesis indirectly by correcting insulin resistance and reducing adiposity. Contemporary molecular syntheses also discuss interactions between incretin signaling and steroidogenic pathways, including gonadotropin-responsive signaling and enzymes involved in steroid hormone production [1].

Nevertheless, direct steroidogenic effects should not be overstated. The direction of a pathway observed in cultured cells may not translate to a clinically meaningful change in intact human ovaries. Dose, exposure duration, metabolic phenotype, species, follicular stage, and concomitant treatments can all modify experimental responses. The safest interpretation is that GLP-1 signaling is biologically capable of interacting with ovarian steroidogenic pathways, while the magnitude and clinical significance of that interaction remain uncertain. As with the mechanistic evidence discussed elsewhere in this review, most steroidogenic pathway data derive from single-receptor GLP-1RA exposure; the incremental or distinct contribution of the additional GIP pathway engaged by dual agonists such as tirzepatide to ovarian steroidogenesis has not been specifically characterized.

Granulosa-oocyte communication

The oocyte develops within a specialized follicular microenvironment rather than in isolation. Gap junctions and

paracrine signaling permit exchange of metabolites and regulatory signals between the oocyte and surrounding cumulus/granulosa cells. Consequently, a therapy that improves granulosa-cell function could theoretically influence the conditions under which the oocyte matures even if the drug has no direct action on the oocyte.

The CXCL10/GJA1 observations are particularly relevant because connexin-43-mediated communication is integral to follicular coordination [13]. However, the translational gap remains large. Human oocyte competence encompasses nuclear maturation, cytoplasmic maturation, mitochondrial function, chromosomal segregation, and the capacity to support embryo development. A change in a granulosa-cell inflammatory marker cannot by itself establish improvement in any of these endpoints.

Immunological effects and endometrial receptivity

Obesity-related infertility and recurrent pregnancy loss (RPL) are not purely endocrine phenomena; obesity also disrupts immune tolerance mechanisms and endometrial receptivity through chronic low-grade inflammation. A 2025 review proposed that GLP-1-based therapies may offer immunological, in addition to metabolic and vascular, benefits relevant to infertility and RPL, potentially improving pregnancy outcomes by modulating immune factors in obese women during a defined preconception window [21]. As with the granulosa-cell and follicular data discussed above, this immunological framework is mechanistically plausible but remains an emerging research hypothesis rather than an established clinical indication, and it reinforces rather than supersedes the existing caution regarding use during pregnancy [21].

Figure 2 summarizes the most coherent clinical model. In women

with obesity-related PCOS, GLP-1RA treatment can improve energy balance and metabolic health; these changes may reduce hyperinsulinemia and androgen-related dysfunction, improve cycle characteristics, and create a more favorable preconception environment. Direct ovarian signaling may contribute, but current evidence does not allow its effect to be separated reliably from systemic metabolic improvement.

Oocyte-Related Biology: What Can and Cannot Be Claimed

The phrase “oocyte quality” is widely used clinically but encompasses multiple biological dimensions. These include meiotic competence, spindle integrity, chromosome segregation, mitochondrial function, cytoplasmic maturation, and the ability of the resulting embryo to develop. In human IVF, clinically relevant proxies may include mature oocyte rate, fertilization rate, blastocyst formation, euploidy, implantation, cumulative live birth, and time to pregnancy. Euploidy in particular should not be treated as synonymous with oocyte competence: a euploid embryo is an important endpoint, but embryo developmental competence is not fully captured by euploidy, and euploidy itself is an embryo-level endpoint rather than a direct measure of intrinsic oocyte quality. The more defensible endpoint sequence runs from oocyte endpoints through fertilization, embryo development, euploidy, implantation, ongoing pregnancy, and live birth. A therapy that improves one intermediate endpoint does not necessarily improve all downstream endpoints.

The current GLP-1RA literature does not establish a direct improvement in human oocyte competence. Experimental studies provide plausible mechanisms through the follicular environment, inflammatory signaling, and granulosa-oocyte communication,

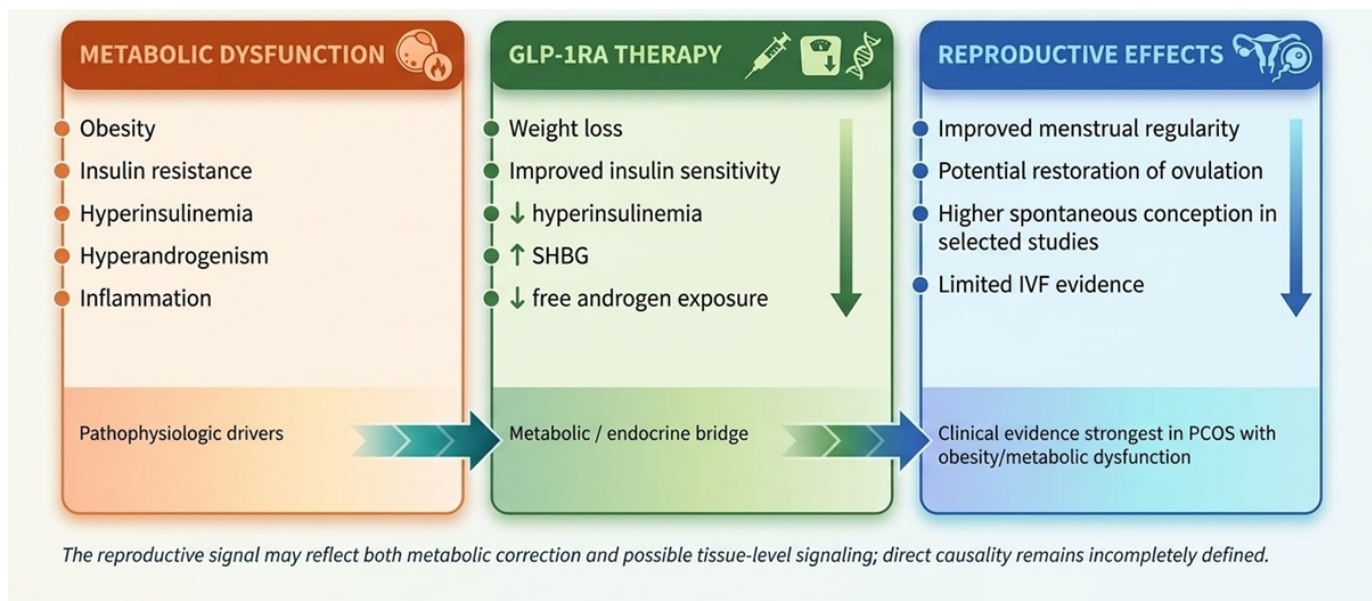


Figure 2: Metabolic dysfunction → GLP-1RA therapy → reproductive effects in PCOS.

[Source: Conceptual synthesis based on refs. [1-4,7-9,12,13,17-20,22-24]; arrows represent biologically plausible pathways and should not be interpreted as proof of direct causation.]

but there are insufficient prospective human data linking GLP-1RA exposure to oocyte euploidy, mitochondrial competence, embryo quality, or cumulative live birth [1,4,13].

Accordingly, terminology such as “oocyte rejuvenation” should be avoided in an evidence-based review unless directly supported by human reproductive endpoints. A more defensible formulation is that metabolic correction may improve the follicular environment in selected women with obesity or PCOS and that direct ovarian effects remain a research hypothesis. This distinction is not merely semantic; it protects against translating mechanistic plausibility into a therapeutic claim that has not yet been tested adequately.

Clinical Evidence in PCOS

PCOS provides the strongest clinical setting for evaluating GLP-1RAs because the condition integrates metabolic dysfunction, hyperandrogenism, menstrual disturbance, and infertility. Yet PCOS is heterogeneous. Some women are lean and metabolically healthy, whereas others have marked obesity, insulin resistance, dyslipidemia, and type 2 diabetes. The expected contribution of GLP-1RA therapy may therefore differ substantially between phenotypes.

Exenatide randomized trial

Liu and colleagues conducted a 24-week open-label prospective randomized study of 176 overweight or obese women with PCOS. Participants received exenatide 10 µg twice daily or metformin 1000 mg twice daily for 12 weeks; during the subsequent 12 weeks, all participants received metformin [22]. Natural pregnancy during the second 12-week period was higher in the exenatide group, reported as 43.6% versus 18.7%. Because the pregnancy assessment occurred after the GLP-1RA phase and both groups subsequently received metformin, the study supports a possible preconception effect but does not establish a persistent direct ovarian drug effect.

The study is nevertheless important because it demonstrates how treatment sequencing can matter. A medication may improve fertility after it has been stopped if the metabolic and endocrine changes it produced persist. Therefore, the correct clinical question is not necessarily “Does the drug increase pregnancy while present in the bloodstream?” but rather “Can a period of metabolic treatment improve the probability of successful conception after transition to pregnancy-compatible care?”

Long-term follow-up

Li and colleagues subsequently reported long-term follow-up of 160 overweight or obese women with infertility and PCOS who had been randomized to exenatide or metformin for 12 weeks. Afterward, all participants received metformin; assisted reproduction could be offered if spontaneous conception did not occur [23]. By week 24, spontaneous conception occurred in 29.2% of the exenatide group versus 14.7% of the metformin group. By week 64, however, total pregnancy rates were 79.2% versus 76.0%, respectively, without a statistically significant difference.

The changing effect over time is highly informative. An early difference in spontaneous conception does not necessarily translate into a durable difference in overall pregnancy when subsequent fertility treatment is available. This pattern argues for reporting cumulative live birth and time-to-pregnancy outcomes rather than relying solely on short-term pregnancy rates. It also reinforces the hypothesis that GLP-1RA therapy may function as a preconception metabolic optimization period rather than a permanent fertility-enhancing therapy.

Liraglutide and menstrual function

The 72-participant randomized liraglutide study provides complementary evidence because it focused on ovarian dysfunction rather than solely on weight or pregnancy [19]. Improved menstrual frequency supports a physiological effect on reproductive function, although the trial was not powered or designed to establish live birth. Together with the exenatide data, it suggests that the reproductive signal is not limited to a single molecule or single endpoint.

Evidence synthesis and heterogeneity

The 2023 meta-analysis by Zhou and colleagues pooled 11 randomized trials involving 840 women with PCOS and reported a higher natural pregnancy rate with GLP-1RA therapy (RR 1.72, 95% CI 1.22–2.43; $I^2=0\%$, indicating low heterogeneity for this outcome) [20]. The same analysis reported an improvement in menstrual cyclicity (SMD 1.72, 95% CI 0.60–2.85), but with substantial heterogeneity ($I^2=95.6\%$) that warrants caution in interpreting the pooled magnitude of this effect, alongside improvements in metabolic outcomes; it did not find a statistically significant overall improvement in IVF pregnancy rate. These results are encouraging but should be interpreted with attention to differences among the included interventions, comparators, sample sizes, and reproductive endpoints.

The newer 2026 systematic review and meta-analysis by Forslund and colleagues was more conservative and was prospectively registered (PROSPERO CRD42024535096). It included 11 randomized trials after screening 9,654 records and found a modest reduction in BMI when GLP-1RAs were used as add-on therapy (mean difference -1.38 kg/m^2 , 95% CI -2.39 to -0.38), a finding explicitly rated as low-certainty evidence under GRADE; evidence for glucose, insulin, hirsutism, and menstrual regularity was graded as insufficient to support conclusions, and no eligible data were identified for quality of life or cost-effectiveness [2]. The difference between this review and earlier positive syntheses illustrates the importance of certainty assessment: an apparently favorable signal may coexist with low certainty because studies are small, heterogeneous, and often not primarily designed around fertility outcomes. Two additional 2024 meta-analyses reached broadly concordant conclusions: one confirmed consistent weight loss and improvements in hormonal parameters with GLP-1 agonists in women with PCOS and obesity, and the other similarly reported metabolic and hormonal benefit while noting that evidence for reproductive-specific endpoints remained less robust

[25,26]. Selected clinical studies and evidence syntheses addressing reproductive outcomes are summarized in Table 1.

Assisted Reproductive Technology and IVF

The IVF literature is smaller than the PCOS metabolic literature. The most frequently cited study is the 2018 pilot randomized trial by Salamun and colleagues, which enrolled 28 infertile women with obesity and PCOS who had previously responded poorly to lifestyle modification and first-line reproductive treatments [24]. Participants received metformin alone or metformin plus low-dose liraglutide for 12 weeks, followed by a 4-week medication-free interval before ovarian stimulation.

The investigators reported pregnancy per embryo transfer of 85.7% in the liraglutide-plus-metformin group versus 28.6% with metformin alone. Cumulative pregnancy over 12 months was 69.2% versus 35.7% [24]. Importantly, both groups experienced comparable weight loss, which led the authors to propose that mechanisms beyond weight reduction might contribute. The study therefore provides an intriguing signal for a direct or indirect reproductive effect that is not completely explained by weight change.

However, the study has major limitations. The sample was extremely small, participants were highly selected, the study was open-label, and the pregnancy endpoint was pregnancy per embryo transfer rather than cumulative live birth. Most importantly, ovarian stimulation began after the 4-week medication-free interval [24]. Thus, the study does not support active GLP-1RA administration during controlled ovarian stimulation. Instead, it is better interpreted as evidence that a preconception intervention preceding IVF may alter subsequent reproductive outcomes in a selected phenotype.

Current PCOS guidance continues to place established ovulation-induction and IVF strategies within a defined treatment algorithm [9]. GLP-1RAs should therefore not be positioned as substitutes for letrozole, gonadotropins, or IVF. Their potential value lies in addressing metabolic barriers before reproductive treatment, especially when obesity is severe enough to affect fertility, pregnancy risk, or access to treatment.

Endometrial, Implantation, and Uterine Considerations

The endometrium is another potential mediator of the association between metabolic health and fertility. Obesity and insulin resistance are associated with altered endometrial signaling, inflammation, and implantation biology. However, the clinical GLP-1RA literature has not established a direct improvement in human endometrial receptivity. The 2018 IVF pilot study raised the possibility that endometrial quality might contribute to its observed pregnancy difference, but this was a hypothesis rather than a mechanistically proven finding [24].

Two recent reviews have addressed this question directly. One synthesized emerging evidence suggesting that GLP-1RAs may influence endometrial gene expression and receptivity markers, proposing a previously underappreciated uterine mechanism that could contribute to implantation outcomes independent of oocyte or embryo quality [27]. A companion analysis cautioned that this endometrial signal remains preliminary and urged a safety-first approach to reproductive and endometrial research in this area before any clinical extrapolation is made [28].

This distinction is important in IVF research. A higher pregnancy rate could theoretically result from changes in embryo quality, endometrial receptivity, implantation, luteal function, or selection effects. Future trials should therefore report mature oocyte number,

Table 1: Selected clinical evidence on GLP-1RA therapy and female reproductive outcomes, with Oxford Centre for Evidence-Based Medicine (OCEBM) levels indicated for each individual study. The table deliberately separates study design and endpoint so that pregnancy, menstrual function, and metabolic outcomes are not conflated.

Study / evidence level	Population / design	Main reproductive finding	Treatment timing	Primary endpoint	Interpretation
Nylander et al., [19] OCEBM Level 1b	72 women with PCOS; double-blind randomized trial	Improved menstrual frequency with liraglutide	During active treatment (16 weeks)	Menstrual frequency (ovarian function)	Supports menstrual/ovarian effect; not a live-birth trial
Liu et al., [22] OCEBM Level 1b	176 overweight/obese women with PCOS; randomized trial	Natural pregnancy 43.6% vs 18.7% during post-treatment metformin phase	Post-treatment (subsequent metformin-only phase)	Natural pregnancy rate	Suggests preconception benefit; timing limits direct-drug inference
Salamun et al.,[24] OCEBM Level 1b	28 infertile obese women with PCOS; pilot randomized study	Pregnancy per embryo transfer 85.7% vs 28.6%	Preconception; IVF stimulation began after washout	Pregnancy per embryo transfer	Large signal but very small, selected sample
Li et al., [23] OCEBM Level 1b	160 overweight/obese infertile women with PCOS; long-term follow-up	Spontaneous conception by week 24: 29.2% vs 14.7%; week 64 total pregnancy: 79.2% vs 76.0%	During and after treatment (long-term follow-up)	Spontaneous conception / total pregnancy rate	Early advantage not maintained in total pregnancy rate
Zhou et al., [20] OCEBM Level 1a	11 RCTs; 840 women with PCOS	Natural pregnancy RR 1.72 (95% CI 1.22–2.43)	Heterogeneous across pooled trials	Natural pregnancy rate (pooled)	Favorable signal, but heterogeneity and certainty limitations
Forslund et al., 2026 [2] OCEBM Level 1a	11 RCTs; systematic review/meta-analysis	Modest BMI reduction; insufficient evidence for several reproductive endpoints	Heterogeneous across pooled trials	BMI change; reproductive endpoints (pooled)	More conservative assessment of evidence certainty

fertilization, blastocyst formation, euploidy where applicable, endometrial parameters, implantation, clinical pregnancy, ongoing pregnancy, and cumulative live birth separately. Without such granular reporting, it is difficult to identify where in the reproductive sequence a GLP-1RA-associated benefit occurs.

Preconception Management and Timing of Therapy

The emerging evidence supports a model in which GLP-1RAs may be most useful during a defined preconception interval rather than during attempts to maintain pregnancy. This approach aligns with the physiology of obesity treatment: metabolic improvement may require time, and the reproductive system may benefit from sustained correction of insulin resistance and weight-related endocrine disturbances [17,18].

Timing becomes particularly important in women pursuing IVF. A reasonable research model is a metabolic optimization phase followed by a planned medication transition, a washout interval appropriate to the specific agent, and then ovarian stimulation and embryo transfer. The optimal interval is not established for all GLP-1RAs, and existing trials do not provide a universal protocol. The interval should therefore be based on current product labeling and individualized reproductive planning rather than extrapolated from one small trial.

The clinical decision must also account for age and ovarian reserve. A prolonged weight-loss intervention may be metabolically beneficial but could delay fertility treatment in a woman with declining reproductive potential. Contemporary fertility reviews emphasize this tension: treatment plans should balance the benefits of metabolic optimization against the time-sensitive nature of female fertility [17,18]. The appropriate goal is not maximal weight loss at any cost, but sufficient optimization to improve health and treatment feasibility without creating unnecessary reproductive delay.

Pregnancy and Reproductive Safety

Regulatory position

Beyond reproductive-specific considerations, GLP-1 receptor agonists as a drug class carry a broader documented safety profile. A 2024 review synthesizing 22 studies (5 case reports, 5 randomized controlled trials, 9 real-world cohort analyses, 2 meta-analyses, and 1 systematic review with meta-analysis) described serious adverse events spanning anaphylaxis, cardiovascular, gastrointestinal, psychiatric, and thyroid-related categories, while noting that findings across studies were inconsistent, with some reporting significant associations and others finding none, underscoring that this general-population safety signal warrants clinical vigilance independent of reproductive status rather than a settled causal conclusion [29]. Potential reproductive benefit before conception must be clearly separated from safety during pregnancy. Current U.S. labeling for semaglutide-containing Wegovy states that it may cause fetal harm and recommends discontinuation at least 2 months before a planned pregnancy because of the long half-life of semaglutide [30]. Tirzepatide-containing Zepbound labeling states that the drug may cause fetal harm and should be discontinued

when pregnancy is recognized. It also advises women using oral hormonal contraceptives to switch to a non-oral method or add a barrier method for 4 weeks after treatment initiation and for 4 weeks after each dose escalation because delayed gastric emptying can affect oral contraceptive absorption [31].

These labeling recommendations should be distinguished from the observational human literature. Regulatory warnings incorporate preclinical developmental findings and the absence of adequate controlled pregnancy trials; they are not equivalent to proof that inadvertent exposure inevitably causes harm. Conversely, reassuring observational studies cannot establish that intentional treatment during pregnancy is safe because exposure is confounded by the underlying diseases for which these medications are prescribed.

Emerging human pregnancy data

Evidence is expanding. A large multicentre observational cohort study drawing on six Teratology Information Services databases followed 168 pregnancies with first-trimester GLP-1RA exposure alongside 156 pregnancies of women with diabetes exposed to a non-GLP-1RA antidiabetic agent and 163 pregnancies of overweight or obese women without diabetes; major birth defects occurred in 2.6% of GLP-1RA-exposed pregnancies versus 2.3% of the diabetes reference group (adjusted OR 0.98), providing additional reassurance regarding major malformation risk, although the number of exposed pregnancies remained small for individual agents and stratified analyses [32]. A complementary pharmacovigilance analysis of the FDA Adverse Event Reporting System identified 354 pregnancy-related cases generating 1,671 adverse drug reaction reports between 2004 and 2023, with an exponential rise in reporting since 2012 and a median maternal age of 36 years (50.6% classified as advanced maternal age); the analysis characterized the reported safety profile of GLP-1RA use in pregnancy without identifying a disproportionate signal for major adverse outcomes, while underscoring the well-recognized limitations of spontaneous-reporting pharmacovigilance data, including reporting bias, lack of a denominator population, and inability to establish causality [33]. A 2025 systematic review and meta-analysis of six studies evaluating preconception or first-trimester GLP-1RA exposure did not identify statistically significant differences in several major pregnancy outcomes, although the evidence remained limited and heterogeneous [34]. A 2026 systematic review and meta-analysis including seven cohort studies and more than 40,000 exposed pregnancies similarly reported no statistically significant increase in overall congenital malformations or major congenital malformations after GLP-1RA exposure [35]. These findings are reassuring but should not be interpreted as establishing medication safety during pregnancy. Class-level conclusions regarding pregnancy safety should be interpreted cautiously because available human exposure data combine agents with different molecular structures, pharmacokinetic profiles, indications, and exposure durations.

The appropriate interpretation is one of uncertainty reduction rather than proof of safety. Observational pregnancy studies are

vulnerable to confounding by obesity, diabetes, PCOS, maternal age, concomitant medications, and differences in healthcare utilization. Moreover, the number of exposed pregnancies for individual agents may remain too small to exclude moderate increases in rare outcomes. Prospective pregnancy registries and large linked-data studies remain essential.

Lactation

Lactation represents another evidence gap. Human data on drug concentrations in breast milk, infant exposure, and effects on milk production remain limited for many GLP-1RAs. A systematic review addressing GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation identified only 39 eligible records overall (9 theoretical extrapolations from drug properties, 7 human studies, and 23 animal studies), corresponding to 76 human offspring with any reported outcome data; human lactation data were limited to a single reported subject showing no significant maternal-to-fetal transfer several hours after dosing, while animal data confirmed excretion into breast milk. This sparse evidence base led the authors to conclude that current data are insufficient to characterize offspring outcomes following lactational exposure, reinforcing the recommendation for a cautious, individualized approach [36]. Current labeling and contemporary reviews therefore support a cautious approach rather than routine use during breastfeeding [30,31]. The clinical decision should consider the indication for therapy, the intensity of metabolic disease, breastfeeding goals, alternative treatments, and the possibility of another pregnancy.

Contraception and unintended pregnancy

Improved ovulatory function can have an unintended consequence: a woman previously experiencing anovulation may regain fertility before she recognizes that her reproductive potential has changed. This is clinically relevant for women who do not wish to conceive. Tirzepatide adds a pharmacokinetic consideration because of its

effect on oral medication absorption [31]. Contraceptive counseling should therefore be integrated into GLP-1RA prescribing for reproductive-aged women rather than treated as an afterthought.

Preclinical Evidence and Translational Interpretation

Preclinical evidence is valuable because it can reveal pathways that are difficult to study directly in humans. In ovarian models, investigators have examined follicular growth, granulosa-cell proliferation and survival, inflammatory signaling, steroidogenesis, oxidative stress, and ovulation-related genes. Recent synthesis suggests that effects can differ according to metabolic state, dose, treatment duration, species, and experimental system [1].

The correct translational sequence is therefore: mechanistic plausibility → reproducible experimental phenotype → human biomarker association → prospective clinical endpoint. GLP-1RA reproductive research has progressed through the first two stages and, for some outcomes, the third. It has not yet produced definitive evidence for all clinically important endpoints, particularly cumulative live birth and direct oocyte competence.

This hierarchy also explains why apparently contradictory findings can coexist. A treatment can reduce inflammation in a PCOS granulosa-cell model while producing a different phenotype in an animal model with a different metabolic background. Such findings are not necessarily mutually exclusive; they may indicate that GLP-1 signaling interacts with the pre-existing biological state of the reproductive tissue.

Figure 3 highlights a central conclusion of this review: the most clinically mature evidence concerns metabolic and selected reproductive outcomes in women with PCOS, whereas direct ovarian and oocyte mechanisms are supported mainly by cellular and animal work. The research priority is therefore not simply to

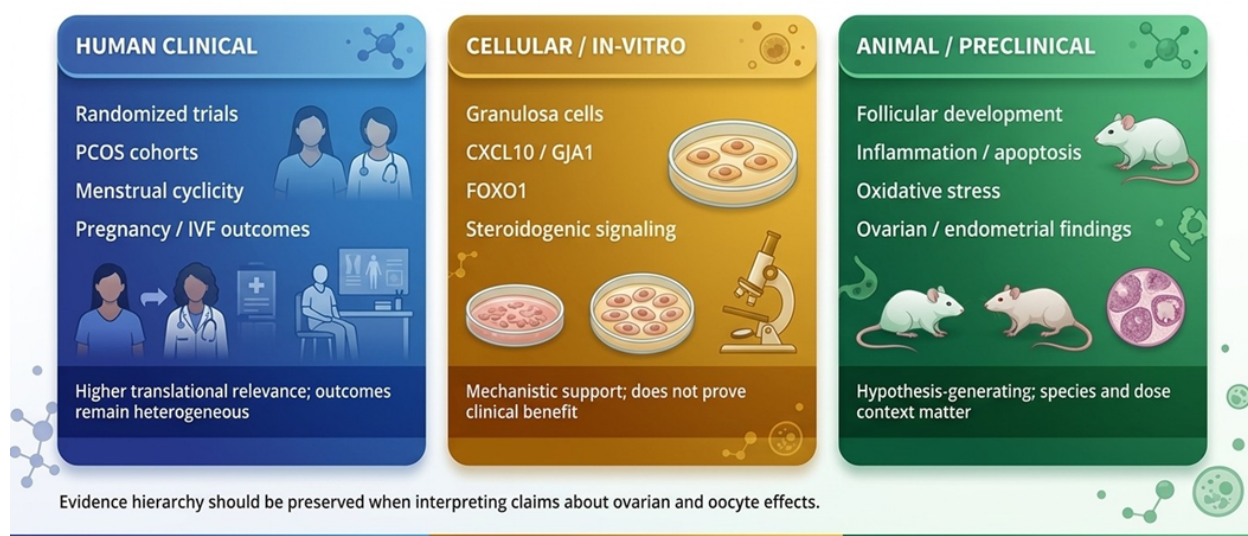


Figure 3: Evidence map: human clinical, cellular/follicular, and animal evidence.

Source: Conceptual evidence hierarchy based on refs. [1-4,12,13,17-20,22-24,34-35]; the figure emphasizes evidence type and translational distance, not a quantitative risk-of-bias score.

generate more mechanistic studies, but to connect mechanistic biomarkers with prospective human reproductive endpoints.

Limitations of the Underlying Evidence

Several limitations constrain interpretation of the current literature. First, many studies enroll women with PCOS and overweight or obesity, so generalizability to lean PCOS, non-PCOS infertility, diminished ovarian reserve, endometriosis, tubal infertility, and unexplained infertility is uncertain. Second, reproductive outcomes are often secondary endpoints in metabolic studies, which means sample sizes and follow-up periods may be inadequate for fertility questions.

Third, studies use different GLP-1RAs, doses, durations, and comparators. Liraglutide and exenatide dominate the older reproductive literature, while semaglutide and tirzepatide are increasingly important clinically [4,19,22,24]. The biological effects of these agents should not be assumed to be identical: tirzepatide is a dual GIP/GLP-1 receptor agonist rather than a single-receptor GLP-1RA, and even among true GLP-1RAs, molecular structure, receptor affinity, and pharmacokinetics differ.

Fourth, treatment timing complicates causal inference. If pregnancy occurs after discontinuation, the effect may reflect persistent metabolic improvement rather than ongoing pharmacological receptor stimulation. Fifth, pregnancy rate is not synonymous with live birth. A therapy could change conception without changing cumulative live birth, as illustrated by the long-term exenatide follow-up [23].

Sixth, mechanistic studies frequently rely on cultured granulosa cells or animal follicles. These systems cannot reproduce the complete human ovarian environment, endocrine feedback, vascular supply, immune interactions, or age-related changes. Seventh, the literature contains limited information on ovarian reserve markers, follicle number dynamics, oocyte aneuploidy, embryo development, cumulative live birth, and long-term offspring outcomes. These are not minor omissions; they are central to determining whether a therapy genuinely improves reproductive potential.

Limitations of this Review

The limitations described above concern the underlying primary and secondary literature. A separate set of limitations concerns the design of this review itself and should be weighed independently by the reader.

First, this is a narrative rather than a systematic review. Although the search strategy, inclusion and exclusion criteria, and evidence-grading framework described in the Review Approach and Scope section were applied to improve transparency, study identification and selection were not performed in duplicate by independent reviewers, and no registered protocol (e.g., PROSPERO) governed this synthesis. This contrasts with several of the systematic reviews and meta-analyses cited here, which followed registered, duplicate-reviewer protocols.

Second, no formal study-level risk-of-bias instrument (e.g., Cochrane RoB 2, ROBINS-I, or Newcastle-Ottawa Scale) was applied by the authors to each individual primary study; the GRADE and OCEBM classifications used in this review were applied at the level of pooled clinical endpoints and individual study designs respectively, drawing where possible on risk-of-bias and certainty assessments already reported by the source systematic reviews rather than on an independent re-assessment conducted de novo for this manuscript.

Third, this review was conducted and written by its own author group rather than by an independent editorial or methodological team, and all co-authors are founding members of the Global Organization of Gonadal Bioregeneration (GOGB), several holding specific executive or committee roles within it, the organization under whose executive board this review is published; the Conflicts of Interest section above addresses this affiliation explicitly. While no financial conflict is declared, authorship by investigators active in this field carries an inherent risk of interpretive bias that an external systematic review process is designed to reduce.

Fourth, the literature search, while structured and documented, was conducted by the authors rather than by an information specialist or librarian, which may have introduced search-strategy blind spots compared with a librarian-mediated systematic search. Fifth, because the reproductive GLP-1RA literature is expanding rapidly, some relevant studies published close to the September 2026 search closure date may not have been captured.

These review-level limitations do not invalidate the synthesis presented here, but they should inform how much interpretive weight readers place on this review relative to the registered systematic reviews and meta-analyses it cites, and they are disclosed so that readers and editors can weigh the manuscript's conclusions accordingly.

Comparison with Established Fertility Management

GLP-1RA therapy should be integrated with, not substituted for, established fertility management. In anovulatory PCOS without other infertility factors, the 2023 international guideline identifies letrozole as first-line pharmacological ovulation induction [9]. Metformin can have a role in selected patients, particularly where metabolic indications coexist, but it is less effective for ovulation induction than letrozole. The presence of obesity or insulin resistance may justify metabolic treatment in parallel with fertility care, but the sequence should be individualized.

For women proceeding to IVF, the role of GLP-1RAs is even less established. The small Salamun trial suggests that preconception liraglutide plus metformin may improve pregnancy outcomes in a highly selected group, but this should be considered hypothesis-generating rather than a basis for routine IVF protocols [24]. Current evidence does not establish that GLP-1RA exposure during ovarian stimulation improves oocyte yield, embryo competence, implantation, or live birth.

This distinction also protects against a common therapeutic misconception: because a medication improves body weight and menstrual regularity, it does not automatically follow that the medication improves every stage of reproduction. A rational treatment plan should identify the dominant infertility mechanism in each patient and use GLP-1RA therapy only when its metabolic indication and reproductive timing are justified.

Proposed Clinical Framework for Reproductive-Aged Women

A practical clinical framework for integrating GLP-1RA therapy with reproductive planning is presented in Table 2. The approach emphasizes individualized assessment of the indication for obesity and PCOS management, reproductive goals, contraception, anticipated pregnancy timing, and transition to pregnancy-compatible metabolic management when conception is planned or pregnancy occurs. In women with PCOS and anovulation, GLP-1RA therapy may have a role in preconception metabolic optimization, particularly when obesity or metabolic dysfunction is present, and available evidence suggests potential improvements in menstrual cyclicity and spontaneous conception; however, these findings should not be interpreted as establishing GLP-1RAs as fertility treatments or substitutes for evidence-based ovulation induction [18-20]. In anovulatory PCOS, established fertility management should remain the basis of ovulation induction, with letrozole identified as the first-line pharmacological treatment in the 2023 international guideline [9]. For women preparing for IVF, GLP-1RA therapy should similarly be regarded as a time-limited, individualized preconception intervention rather than an established method for improving IVF outcomes, oocyte competence, or embryo quality. The small randomized pilot study of preconception liraglutide plus metformin reported a higher IVF pregnancy rate, but the limited sample size and post-treatment ovarian stimulation design make the finding hypothesis-generating rather than sufficient to support routine IVF protocols [24].

The current strength of evidence across metabolic and reproductive outcomes is summarized in Table 3, which distinguishes the well-established role of GLP-1RAs in weight and metabolic optimization from the more limited and uncertain evidence for spontaneous

conception, IVF outcomes, oocyte competence, embryo euploidy, and live birth [1,2,20]. Importantly, improved menstrual regularity should not be equated with confirmed ovulation, pregnancy should not be equated with live birth, and embryo euploidy is an embryo-level rather than a direct measure of intrinsic oocyte competence. Consequently, current evidence does not support claims of direct improvement in human oocyte quality, embryo euploidy, or cumulative live birth [1,2,4,20]. Reproductive planning must also incorporate contraception and agent-specific discontinuation requirements. Current U.S. prescribing information cited in this review recommends discontinuation of semaglutide at least 2 months before planned pregnancy, while tirzepatide should be discontinued when pregnancy is recognized; therefore, potential preconception metabolic benefits must be clearly distinguished from intentional pharmacological exposure during pregnancy [30,31]. Emerging observational pregnancy data are reassuring in some respects but remain insufficient to establish routine pregnancy safety, supporting the individualized, time-dependent clinical framework summarized in Tables 2 and 3 [32-35].

Table 3: Clinical bottom line: current strength of evidence and practical interpretation by clinical question. This summary is intended to support patient counseling and does not substitute for individualized clinical judgment.

Clinical question	Current evidence	Practical interpretation
Weight loss / metabolic optimization	Strong	Established indication
Menstrual regularity in PCOS	Moderate	Potential reproductive benefit; not proof of ovulation
Spontaneous conception	Suggestive	Promising but not definitive; heterogeneous evidence
Ovulation induction	Insufficient	Not a substitute for letrozole
IVF outcomes	Very limited	Hypothesis-generating only
Oocyte competence	Insufficient	Do not claim direct benefit
Embryo euploidy	Insufficient	Unknown; an embryo-level, not oocyte-level, endpoint
Live birth	Insufficient	Major evidence gap
Pregnancy safety	Reassuring but low certainty	Avoid intentional exposure; follow current labeling
Lactation	Limited	Individualized decision

Table 2: Practical framework for integrating GLP-1RA therapy with reproductive planning. This is a conceptual framework derived from current evidence and prescribing information, not a substitute for individualized clinical judgment.

Clinical situation	Potential role of GLP-1RA	Key considerations
Obesity with no immediate pregnancy plan	Potential metabolic therapy	Assess long-term obesity indication, reproductive goals, contraception, and future pregnancy timing
Obesity + PCOS + anovulation	Potential preconception metabolic optimization	Do not substitute for evidence-based ovulation induction; monitor menstrual/ovulatory recovery
PCOS preparing for IVF	Potential time-limited preconception intervention	Coordinate with fertility team; plan discontinuation and washout; avoid assuming active-treatment benefit
Actively attempting conception	Generally requires transition away from GLP-1RA therapy	Use agent-specific labeling; avoid unplanned exposure; maintain metabolic management with pregnancy-compatible strategies
Pregnancy recognized while taking GLP-1RA	Stop and contact treating clinician	Follow current product labeling and individualized obstetric/diabetes management
Breastfeeding	Evidence limited	Balance indication, lactation goals, alternatives, and future pregnancy plans

Research Priorities

Future trials should be designed around reproductive questions rather than treating fertility as an incidental secondary endpoint. First, randomized studies should compare GLP-1RAs with lifestyle intervention, metformin, or standard metabolic care while measuring ovulation, conception, ongoing pregnancy, and live birth. Second, trials should stratify participants by BMI, insulin resistance, PCOS phenotype, age, and ovarian reserve so that treatment effects are not diluted across biologically distinct populations.

Third, studies should separate preconception exposure from active ovarian stimulation. This distinction is essential because the available IVF pilot study began stimulation after a medication-free interval [24]. Fourth, fertility trials should measure oocyte and embryo endpoints, including mature oocyte rate, fertilization, blastocyst development, euploidy when tested, implantation, cumulative live birth, and time to pregnancy.

Fifth, translational studies should connect follicular-fluid biomarkers such as CXCL10 with granulosa-cell signaling and clinical outcomes. A biomarker that changes with treatment becomes much more informative if the magnitude of change predicts follicular development or embryo competence. Sixth, large pregnancy registries should continue to collect data on inadvertent exposure, miscarriage, congenital anomalies, fetal growth, preterm birth, hypertensive disorders, and neonatal outcomes [34,35].

Finally, research should expand beyond PCOS and obesity. If direct ovarian actions exist, they may be detectable in metabolically healthy women; if they do not, the field should explicitly define GLP-1RAs as metabolic rather than ovarian therapies. This distinction will improve both scientific clarity and clinical counseling. Patient-reported perspectives also deserve systematic attention: an investigational pilot survey conducted in an academic reproductive endocrinology setting found that patients' understanding of GLP-1RA use around fertility care is still evolving, underscoring a need for structured patient-centered outcomes research and clearer counseling frameworks alongside the biological research agenda outlined above [5].

Discussion

Taken together, the evidence supports a layered interpretation of GLP-1RA reproductive effects. The first layer is metabolic: reduced energy intake and improved glucose-insulin physiology can alter the endocrine environment that supports reproduction. The second layer is reproductive-endocrine: changes in insulin, androgen availability, SHBG, and menstrual cyclicity may restore more regular ovarian function. The third layer is local ovarian biology: experimental evidence suggests that GLP-1 signaling can influence granulosa-cell inflammatory pathways, follicular development, and intercellular communication [1,13].

The relative importance of these layers is likely phenotype dependent. In women with marked obesity and insulin resistance,

metabolic restoration may account for much of the reproductive improvement. In women whose weight loss is modest but whose reproductive endpoints change, direct or indirect ovarian effects become more plausible, although not proven. The available evidence does not justify choosing between these mechanisms as mutually exclusive alternatives; a synergistic model is more consistent with current data.

The strongest clinical argument for GLP-1RAs is therefore not that they “increase fertility” in a universal sense. It is that they can improve a metabolic state that is itself associated with reproductive dysfunction. In selected women with obesity-related PCOS, this may increase the probability of spontaneous ovulation and conception and may improve readiness for fertility treatment. The evidence becomes much weaker when the claim is extended to direct oocyte rejuvenation, improved euploidy, enhanced implantation, or improved cumulative live birth.

Safety further constrains the therapeutic model. The same medications that may improve reproductive function before conception should generally be discontinued when pregnancy is recognized, and semaglutide requires a longer planned preconception interval under current U.S. labeling [30,31]. Emerging observational pregnancy data are reassuring enough to justify continued study but not strong enough to reverse current labeling-based practice. This apparent paradox—possible preconception benefit alongside pregnancy avoidance—is not unusual in reproductive medicine and should be communicated clearly to patients.

Conclusions

GLP-1 receptor agonists occupy an increasingly important position at the intersection of metabolic and reproductive medicine. The most consistent human evidence supports their ability to improve body weight and metabolic health, with selected randomized trials demonstrating improvements in menstrual function and short-term spontaneous pregnancy among women with PCOS and overweight or obesity [19-23]. A small IVF pilot study further suggests that preconception liraglutide plus metformin may improve pregnancy outcomes in a highly selected population, although its small sample and post-treatment stimulation design prevent broad generalization [24].

At the mechanistic level, GLP-1 signaling may influence reproductive biology through both systemic metabolic restoration and local ovarian pathways. Experimental evidence involving granulosa-cell inflammation, CXCL10, JAK signaling, connexin-43, follicular development, and steroidogenic pathways provides a plausible biological framework [1,13]. Yet receptor localization or cellular pathway modulation does not prove improved human oocyte competence. Claims of oocyte rejuvenation, improved euploidy, or enhanced embryo developmental potential remain unsupported by sufficiently robust human evidence.

The most defensible clinical model is therefore individualized and time dependent. GLP-1RAs may be useful as preconception

metabolic optimization for selected women with obesity-related reproductive dysfunction, particularly PCOS, while established fertility therapies remain the basis of ovulation induction and assisted reproduction. Reproductive goals, contraception, treatment timing, medication-specific discontinuation requirements, and pregnancy safety should be addressed before therapy begins. Large prospective studies that connect metabolic change, ovarian biomarkers, oocyte and embryo endpoints, and cumulative live birth are required before GLP-1RAs can be considered established fertility therapies.

Acknowledgments

During the preparation of this manuscript, the authors used Claude (Anthropic) to assist with targeted literature retrieval and verification, reference formatting, and renumbering of in-text citations and the reference list according to Vancouver style following incorporation of peer-review comments. The tool was also used to support editorial refinement of selected sections in response to those comments. All AI-assisted output was reviewed, fact-checked, and edited by the authors, who take full responsibility for the accuracy, integrity, and scientific content of the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest. All authors are founding members of the Global Organization of Gonadal Bioregeneration (GOGB), the organization under whose executive board this review is published, and several hold specific formal roles within it: Carmen Teresa Navarro (World President); Panayiotis Michael Zavos (Co-founder and Managing/Executive Director); Pedro Torrecillas Cabrera (Vice President of Gonadal Bioregeneration and Director of the Male Regeneration Committee); Cesare Aragona (Director of the European Scientific and Academic Committee); Maria Salomé Bezerra-Espínola (Coordinator of Basic Research and International Academic Relations); Denisa Protopopescu (Co-founder and Director of Clinical Development for Eastern Europe); and Ritu Santwani (Executive Director and Regional Medical Representative for Asia and the Middle East). The GOGB did not provide financial support for this work, did not influence its scientific content, and had no role in the design of the review, the interpretation of the evidence, or the decision to publish. The authors declare that this organizational affiliation does not constitute a competing interest and is disclosed here in the interest of full editorial transparency.

References

1. Voros C, Chatzinikolaou F, Papapanagiotou I, Spyridon Polykalas, Despoina Mavrogianni, et al. A Systematic Review on GLP-1 Receptor Agonists in Reproductive Health: Integrating IVF Data, Ovarian Physiology and Molecular Mechanisms. *Int J Mol Sci*. 2026; 27: 759.
2. Forslund M, Wändell P, Forsberg L, Marie Österberg, Jessica Dagerhamn, et al. GLP-1 receptor agonist treatment in women with polycystic ovary syndrome-a systematic review and meta-analysis. *Eur J Endocrinol*. 2026; 194: 25-39.
3. Abedi MM, Patni MM, Bint Shajahan AN, Rajani Dube, Liyan Khadeeja, et al. GLP-1 Receptor Agonists, Fertility Restoration, and Reproductive Safety in Women of Reproductive Age: A Narrative Review. *J Clin Med*. 2026; 15: 3204.
4. Becker AS, Castilhos JP, Shugair SAS, Colombo T, Hentschke MR. GLP-1 Receptor Agonists and Fertility: What Is Known So Far? *JBRA Assist Reprod*. 2026; 30: 649-657.
5. Vlasak AL, Lindsey P, Minnihan A, Rhoton-Vlasak A. GLP-1 Receptor Agonists in Reproductive Medicine: A Narrative Review and Investigational Pilot Survey of Patient Perspectives in Academic Reproductive Endocrinology. *Reprod Sci*. 2026; 33: 1199-1211.
6. Pyke C, Heller RS, Kirk RK, Cathrine Ørskov, Steffen Reedtz-Runge, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014; 155: 1280-1290.
7. Armstrong A, Berger M, Al-Safi Z. Obesity and reproduction. *Curr Opin Obstet Gynecol*. 2022; 34: 184-189.
8. Practice Committee of the American Society for Reproductive Medicine. Obesity and reproduction: a committee opinion. *Fertil Steril*. 2021; 116: 1266-1285.
9. Teede HJ, Tay CT, Laven JJE, Anuja Dokras, Lisa Moran J, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *J Clin Endocrinol Metab*. 2023; 108: 2447-2469.
10. Jensterle M, Janez A, Fliers E, DeVries JH, Vrtacnik-Bokal E, et al. The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective. *Hum Reprod Update*. 2019; 25: 504-517.
11. Xie Z, Zheng G, Liang Z, Li M, Deng W, et al. Seven glucagon-like peptide-1 receptor agonists and polyagonists for weight loss in patients with obesity or overweight: an updated systematic review and network meta-analysis of randomized controlled trials. *Metabolism*. 2024; 161: 156038.
12. Couldwell M, Tidwell AJ, Taylor AE. Effect of GLP1 agonists on reproduction. *J Clin Endocrinol Metab*. 2025; 110: 3009-3024.
13. Zhao M, Liao B, Yun C, Qi X, Pang Y. Liraglutide improves follicle development in polycystic ovary syndrome by inhibiting CXCL10 secretion. *Reprod Biol Endocrinol*. 2024; 22: 98.
14. Hunter E, Avenell A, Maheshwari A, Stadler G, Best D. The effectiveness of weight-loss lifestyle interventions for improving fertility in women and men with overweight or obesity and infertility: a systematic review update of evidence from randomized controlled trials. *Obes Rev*. 2021; 22: e13325.
15. Hoek A, Wang Z, van Oers AM, Groen H, Cantineau AEP. Effects of preconception weight loss after lifestyle intervention on fertility outcomes and pregnancy complications. *Fertil Steril*. 2022; 118: 456-462.

16. Ruiz-González D, Cavero-Redondo I, Hernández-Martínez A, Baena-Raya A, Martínez-Forte S, et al. Comparative efficacy of exercise, diet and/or pharmacological interventions on BMI, ovulation, and hormonal profile in reproductive-aged women with overweight or obesity: a systematic review and network meta-analysis. *Hum Reprod Update*. 2024; 30: 472-487.
17. Duah J, Seifer DB. Medical therapy to treat obesity and optimize fertility in women of reproductive age: a narrative review. *Reprod Biol Endocrinol*. 2025; 23: 2.
18. Goldberg AS, Boots CE. Treating obesity and fertility in the era of glucagon-like peptide 1-receptor agonists. *Fertil Steril*. 2024; 122: 211-218.
19. Nylander M, Frøssing S, Clausen HV, Kistorp C, Faber J, Skouby SO. Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial. *Reprod Biomed Online*. 2017; 35: 121-127.
20. Zhou L, Qu H, Yang L, Lan Shou. Effects of GLP1RAs on pregnancy rate and menstrual cyclicity in women with polycystic ovary syndrome: a meta-analysis and systematic review. *BMC Endocr Disord*. 2023; 23: 245.
21. Tavares ACM, Martins MYM, de Souza GF, Eduarda Maia Lima, Camila Alves Rocha, et al. Immunological effects of GLP-1 analogs on female reproduction: Therapeutic perspectives for infertility and recurrent pregnancy loss. *J Reprod Immunol*. 2025; 169: 104538.
22. Liu X, Zhang Y, Zheng SY, Rong Lin, Yi-Juan Xie, et al. Efficacy of exenatide on weight loss, metabolic parameters and pregnancy in overweight/obese polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2017; 87: 767-774.
23. Li R, Mai T, Zheng S, Zhang Y. Effect of metformin and exenatide on pregnancy rate and pregnancy outcomes in overweight or obese infertility PCOS women: long-term follow-up of an RCT. *Arch Gynecol Obstet*. 2022; 306: 1711-1721.
24. Salamun V, Jensterle M, Janez A, Vrtacnik Bokal E. Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. *Eur J Endocrinol*. 2018; 179: 1-11.
25. Morais BAAH, Martins Prizão V, de Moura de Souza M, Ximenes Mendes B, Rodrigues Defante ML, et al. The efficacy and safety of GLP-1 agonists in PCOS women living with obesity in promoting weight loss and hormonal regulation: a meta-analysis of randomized controlled trials. *J Diabetes Complications*. 2024; 38: 108834.
26. Tong X, Song X, Zhang Y, Zhao Q. Efficacy and safety of glucagon-like peptide-1 receptor agonists in the treatment of polycystic ovary syndrome-a systematic review and meta-analysis. *Arch Physiol Biochem*. 2024; 130: 1005-1011.
27. Sola-Leyva A, Pathare ADS, Apostolov A, Aleksejeva E, Kask K, et al. The hidden impact of GLP-1 receptor agonists on endometrial receptivity and implantation. *Acta Obstet Gynecol Scand*. 2025; 104: 258-266.
28. Viganò P, Casalechi M, Salonia A, Somigliana E. Ensuring safety first: GLP-1RAs in reproductive and endometrial research. *Acta Obstet Gynecol Scand*. 2025; 104: 998-999.
29. Tobaiqy M. A review of serious adverse events linked with GLP-1 agonists in type 2 diabetes mellitus and obesity treatment. *Pharmacol Rep*. 2024; 76: 981-990.
30. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215256s033lbl.pdf
31. Eli Lilly Company. Zepbound tirzepatide prescribing information. Revised April 2026. <https://pi.lilly.com/ca/zepbound-ca-pm.pdf>
32. Dao K, Shechtman S, Weber-Schoendorfer C, Diav-Citrin O, Murad RH, et al. Use of GLP-1 receptor agonists in early pregnancy and reproductive safety: a multicentre, observational, prospective cohort study based on the databases of six Teratology Information Services. *BMJ Open*. 2024; 14: e083550.
33. Zhou J, Wei Z, Lai W, Liu M, Wu X. The safety profile of usage of glucagon-like peptide-1 receptor agonists in pregnancy: a pharmacovigilance analysis based on the Food and Drug Administration Adverse Event Reporting System. *Br J Clin Pharmacol*. 2024; 91: 1272-1280.
34. Armstrong BBS, Servidoni ACP, Martin GCC, Guilherme FM, Wellgner Fernandes OA, et al. Evaluation of GLP-1 receptor agonists in obstetrics and perinatal outcomes: a systematic review and meta-analysis. *J Gynecol Obstet Hum Reprod*. 2025; 54: 103046.
35. Uysal N, Horoz E, Gungor M, Timarci I, Sozmen MK, et al. Pregnancy outcomes following maternal GLP-1 receptor agonist exposure: a systematic review and meta-analysis. *Sci Rep*. 2026.
36. Müller DRP, Stenvers DJ, Malekzadeh A, Holleman F, Painter RC, et al. Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes: a systematic review of the evidence. *Front Endocrinol (Lausanne)*. 2023; 14: 1215356.